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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,072	07/14/2006	Douglas E. Brough	253625	7914

23460 7590 03/24/2010

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER
SHEN, WU CHENG WINSTON

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
03/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com
Chgpatent1@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,072	BROUGH, DOUGLAS E.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,39-42,45-48,52 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39-42,45-48,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/12/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim amendments filed on 02/12/210 have been entered.

The declaration by Douglas E. Brough on 12/17/2009 has been entered and considered.

Claims 1-34, 36-38, 43, 44, and 49-51 are cancelled. Claim 35 has been amended. Claims 35, 39-42, 45-48, 52, and 53 are pending and currently under examination.

This application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a Continuation-in-part of US application 10/373,249 filed on 02/24/2003, abandoned on 01/18/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Previous rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), is ***withdrawn*** because Applicant's arguments in combination of claim amendments have been fully considered and found persuasive. Previous rejection of claims 50 and 51 is ***moot*** because the claims have been cancelled.

Amended claim 35 filed 02/12/2010 reads as follows: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a

pharmaceutical composition comprising an a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hathl operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hathl resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Neither Zoghbi et al. nor Falck-Pedersen et al. explicitly teach a serotype 28 adenoviral vector (Ad28) in the context of changing the sensory perception of an animal by gene therapy.

2. Previous rejection of claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005), in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Kovesdi et al.** (US patent 6,821,775, issue date, Nov. 23, 2004), is ***withdrawn*** because Applicant's arguments in combination of claim amendments have been fully considered and found persuasive.

3. Previous rejection of claims 45-48 under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Staecker et al.** (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006), is ***withdrawn*** because Applicant's

arguments in combination of claim amendments have been fully considered and found persuasive.

4. Previous rejection of claims 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Wickham et al.** (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and **Mizuguchi et al.** (Mizuguchi et al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, *Gene Ther.* 9(12):769-76, 2002), is ***withdrawn*** because Applicant's arguments in combination of claim amendments have been fully considered and found persuasive.

The following 103 rejections are necessitated by claim amendments filed on 02/12/2010 by Applicant.

5. Claims 35, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005, filed on 05/18/2000)

and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, *Arch Virol.* 64(3):225-33, 1980).

Amended claim 35 filed 02/12/2010 reads as follows: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hathl operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hathl resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an human atonal associated nucleic acid encoding the polypeptide Hath1 (SEQ ID No: 58, 354 amino acid, columns 127-129) (see lines 25-33, col. 5, and claim 3), and Hath1 is a transcription factor belonging to the basic helix-loop-helix (bHLH) family of proteins (See lines 30-32, col. 1). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is Hath1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al teaches that in a preferred embodiment said vector is an adenovirus vector comprising a cytomegalovirus (CMV) IE promoter sequence and a SV40 early polyadenylation signal sequence (See for instance lines 46-50, column 16, Zoghbi et al.). It is worth noting that, In Example 2 of instant application, the Math1 cDNA, which encodes a mouse atonal-associated factor, is operatively linked to the same cytomegalovirus immediate early (CMV) promoter as disclosed by Zoghbi et al.

Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to changing the sensory perception of an animal by expressing Hath1 recited in claim 35, Zoghbi et al. teach methods of treating an animal, including a human, for treating hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor Hath1 (See for instance, second paragraph, col. 5).

With regard to hes-1 promoter (claim 39 of instant application), Zoghbi et al. teaches that it is also possible, and often desirable, to use promoter or control sequences normally associated with the Math1 gene sequence, provided such control sequences are compatible with the host cell systems or the target cell (See Example 15). In this regard, Zoghbi et al. cites Zine et al., 2001, which taught that Hes1 and Hath1 are expressed in the developing cochlea of inner ears (Zine et al., Hes1 and Hes5 activities are required for the normal development of the hair cells in the mammalian inner ear, *The Journal of Neuroscience*, vol. 21, pp. 4712-4720, 2001).

However, Zoghbi et al. do not explicitly teach subgroup 28 (Ad28) adenoviral vector.

Regarding subgroup 28 adenoviral vector, which is a species of adenovirus belongs to subgroup D adenoviral vector, **Falck-Pedersen et al.** characterized the oncogenic potential of adenoviral vectors of different subgroups (See Table shown below, columns 1-2, Falck-Pedersen et al.), and examined the similarities and differences between various adenovirus groups by

comparing the amino acid similarity and identity between the E1A and E1B gene products of Ad2 (group C), Ad5 (group C), Ad7 (group B), Ad12 (group A), and Ad40 (group F) adenoviruses (See Example 5, Falck-Pedersen et al.). Falck-Pedersen et al. teaches the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.).

			Oncogenic potential		
Subgroup	Hemagglutination groups	Serotypes	Tumors in animals	Transformation in tissue culture	Percentage of G + C in DNA
A	IV (little or no agglutination)	12, 18, 31	High	+	48–49
B	I (complete agglutination of monkey erythrocytes)	3, 7, 11, 14, 16, 21, 34, 35	Moderate	+	50–52
C	III (partial agglutination of rat erythrocytes)	1, 2, 5, 6	Low or none	+	57–59
D	II (complete agglutination of rat erythrocytes)	8, 9, 19, 37, 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36, 37, 38, 39, 42	Low or none	+	57–61
E	III	4	Low or none	+	57–59
F	III	40, 41	Unknown		

Falck-Pedersen et al. teaches that there are limitations on the use of group C adenoviral gene therapy vectors regarding a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the

same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40, column 6, Falck-Pedersen et al.). Falck-Pedersen et al. teaches that the adenoviral classification used in the context of the present invention is that as described above and by Horwitz. As such, a "non-group C adenoviral vector" is based on the serotypic definition, e.g., preferably all of the capsid proteins for such an adenoviral vector originate from a non-group C adenovirus. Thus, the term "non-group C adenoviruses" includes adenoviruses of groups A, B, D, E, and F. Falck-Pedersen et al. teaches that preferred adenoviruses used in the construction of non-group C adenoviral gene transfer vectors of the present invention include Ad12 (group A), Ad7 (group B), Ad30 and Ad36 (group D), Ad4 (group E), and Ad41 (group F). More preferred adenoviruses used in the construction of the non-group C adenoviral gene transfer vectors include those of group B, especially Ad7 (See bridging paragraph, column 7-8, Falck-Pedersen et al., 1998).

Falck-Pedersen et al. teaches that any subtype, mixture of subtypes, or chimeric adenovirus can be used as the source of nucleic acid for the generation of the adenoviral vectors of the present invention, although at least one of the adenoviruses used must be a non-group C adenovirus, and the adenoviral vector must remain a non-group C adenoviral vector as serotypically defined, e.g., such that all of the capsid proteins for such an adenoviral vector originate from a non-group C adenovirus. Thus, for example, a region of a particular non-group C adenovirus, e.g., the E4 region of Ad7, can be replaced with a region of a wild-type group C adenovirus, e.g., the E4 region of Ad2 or Ad5. Such combinations are contemplated to provide a series of recombinant adenoviruses that are immunologically invisible, both with respect to wild-type adenoviruses and currently used adenoviral vectors and those generated in the context of the

present invention. Accordingly, a host requiring ongoing gene therapy can be treated using a succession of different adenoviral gene therapy vectors that are not neutralized by antibodies induced in the host in response to earlier natural adenoviral infections and/or earlier gene therapy treatment using other vectors (See lines 7-27, column 8, Falck-Pedersen et al., 1998).

Related to the teachings by Falck-Pedersen et al., **Bout et al.** teaches that Adenovirus serotypes differ in their natural tropism. The adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E) and serotype 7 (subgroup B) all have a natural affiliation towards lung epithelia and other respiratory tissues. In contrast, serotypes 40 and 41 (subgroup F) have a natural affiliation towards the gastrointestinal tract. The serotypes described, differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. This difference in tropism and capsid protein among serotypes has led to the many research efforts aimed at redirecting the adenovirus tropism by modification of the capsid proteins (See abstract, Bout et al., 2005).

It is worth noting that Bout et al. clearly indicates that adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an *optimal* choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, provided above in this rejection, Falck-Pedersen et al.); and with regard to Group D adenoviral

vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.).

Relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., **Wigand et al.** teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980) and is also similar to other subgroup D adenoviruses. As a consequence of the high degree of DNA/DNA homology between adenovirus types belonging to the same subgroups also DNA restriction patterns of subgroup members should be expected to display similarities (See Discussion, page 232, Wigand et al., 1980).

Furthermore, Falck-Pedersen et al. specifically teaches that *any subtype*, mixture of subtypes, or chimeric adenovirus can be used as the source of nucleic acid for the generation of the adenoviral vectors, and furthermore selecting a species of adenoviral vector from a given subgroup adenoviral vector is considered as a routine optimization for desired viral tropism well known for a skilled artisan in gene therapy, which is evident by the teachings of **Bout et al.** (2005). Pertaining to optimization, Applicant's attention is directed to relevant MPEP section cited below.

2144.05 [R-5] Obviousness of Ranges, See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using Ad28 which is closely related to the preferred Ad36 adenoviral vector belonging to subgroup D to circumvent host immunity taught by the combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al. because (i) the presence of immune response to subgroup C adenovirus prevent efficacious adenovirus vector administration *in vivo,* and Ad36 being a preferred vector of Group D adenoviral vectors, by the teachings of Falck-Pedersen et al., and (ii) adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application, by the teachings of Bout et al., and (iii) Ad28 is a close species to Ad36 among Group D adenoviral vectors, by the teachings of Wigand et al.

As such, the ordinary artisan would have been motivated to use the serotype Ad28 adenoviral vector belonging to subgroup D as a preferred adenoviral vector to deliver nucleic acid sequence encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector.

The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with a natural or engineered coat protein in an Ad28 belonging to adenoviral vector of subgroup D and deliver it to inner ear to generate sensory hair cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998), Bout et al. (US patent 6,913,922, issued on 07/05/2005) and Wigand et al. (*Arch Virol.* 64(3):225-33, 1980) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

6. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005), in view of in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, *Arch Virol.* 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Kovesdi et al.** (US patent 6,821,775, issue date, Nov. 23, 2004).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over

Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Regarding an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region, Kovesdi et al. teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7 and claim 1). Kovesdi et al. also disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promote neovascularization. Kovesdi et al. further discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the Ad28 adenoviral vector that circumvents host immunity taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al. because the presence of immune response to the subgroup C adenoviral vector prevent efficacious adenovirus vector administration *in vivo* and adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural

affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Furthermore, It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., Falck-Pedersen et al., Bout et al., Wigand et al., and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. because the vector taught by combined teachings of Falck-Pedersen et al. Bout et al., Wigand et al., and Kovesdi et al. is able to (i) counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the coat protein, and (ii) circumvent host immunity against adenoviral vector subgroup C.

As such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because of (i) its effectiveness in expressing a gene of interest *in vivo* without provoking host immunity to the adenoviral vector belonging to subgroup D, and (ii) capability of expressing the engineered coat protein in the adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region since Kovesdi et al. discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector; however, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

One of ordinary skill in the art would have reasonable expectation of success in delivering a nucleic acid sequence such encoding Hath1, to inner ear to generate sensory hair cells because the adenoviral vector Ad28 taught by combined teachings of Falck-Pedersen et al.,

Bout et al., and Wigand et al., and Kovesdi et al can be used for proper expression of a exogenous gene such Hath1 due to the presence of deficiency in both E1 and E4 and the presence of a spacer in E4 region.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

7. Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, *Arch Virol.* 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Staecker et al.** (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches such a method wherein a viral vector comprising a nucleic acid sequence encoding a

neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor Hath1.

Regarding a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor, Staecker et al. teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the Ad28 adenoviral vector that circumvents host immunity taught by combined teachings of Falck-Pedersen et al. Bout et al., and Wigand et al. because (i) the presence of immune response to the subgroup C adenoviral vector prevents efficacious adenovirus vector administration *in vivo,* and adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is <u>not</u> the cells of inner cells recited in claim 35 of instant application, by the teachings of Bout et al., It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor Hath1 in the method of changing sensory perception based on the combined teaching of Zoghbi et al., Falck-Pedersen et al., and Staecker et al.

One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because BDNF has been shown by Staecker et al. to support the survival of

auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after hearing loss, the ordinary artisan would be motivated to preserve the auditory neurons which are vital for hearing.

The level of skill in the art is high. One of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using a separate or the same vector in the method taught by Zoghbi et al., Falck-Pedersen et al. Bout et al., and Wigand et al. because of the demonstration that a Ad28 adenoviral vector can circumvent host immunity against subgroup C adenoviral vector by the combined teachings of Falck-Pedersen et al., Falck-Pedersen et al. Bout et al., and Wigand et al., and the demonstration that brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons by the teachings of Staecker et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

8. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, *Arch Virol.* 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Wickham et al.** (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and **Mizuguchi et al.** (Mizuguchi et

al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, *Gene Ther.* 9(12):769-76, 2002).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches an adenoviral vector mediated gene therapy with an alternatively targeted adenovirus.

Regarding an adenoviral vector with altered target cells (claims 52 and 53 of instant application), Wickham et al, teaches that coxsackievirus and adenovirus receptor (CAR) is the receptor for adenovirus serotype 2 and 5, citing (Bergelson et al., Science, 275, 1320-23 (1997) (See lines 35-40, col. 1), and mutations reducing affinity of adenovirus for the CAR protein (See Table 2 and Table 3). Mizuguchi et al. teaches that targeted gene delivery to the tissue of interest by recombinant adenovirus (Ad) vectors is limited by the relatively broad expression of the primary receptor, the coxsackievirus and adenovirus receptor (CAR), and the secondary receptor, αv integrin; and this problem could be overcome by mutating the fiber and penton base, which bind with CAR and αv integrin, respectively.

It would have been obvious to one of ordinary skill in the art to use the Ad 28 adenoviral vector taught by the combined teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to

inner ear of a subject since the vector taught by combined teachings of Zoghbi et al. Falck-Pedersen et al., Bout et al., and Wigand et al. that circumvents host immunity against adenoviral vector of subgroup C. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject taught by Zoghbi et al. because the Ad28 vector taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. not only circumvents host immunity, but also successfully targets adenovirus to different cell types expressing different receptors of an adenoviral vector *in vivo*.

As such, the ordinary artisan would have been motivated to use the vector taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. to deliver nucleic acid encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* in desired target cell types, without provoking host immunity to the Ad28 adenoviral vector.

The level of skill in art of molecular cloning is high. One of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with altered coat protein, and deliver the adenoviral vector to desired target cells in inner ear to generate sensory hair cells because the adenoviral vector comprises engineered coat protein taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. can be used to express therapeutic gene *Hath1* into cells of inner ear taught by combined teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al., and the altered ligand-receptor interaction taught by Wickham et al. and Mizuguchi et al. can result in the

adenoviral virus targeting to desired cells expressing different receptors of an adenoviral vector *in vivo* .

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments and Response to applicant's arguments

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that the 103 rejections documented in the Non-Final office action mailed on 06/18/2009. The amended limitation reciting Ad28 in the claimed methods have been addressed in the new 103 rejections documented in this office action.

Applicant's arguments of unexpected results regarding the enhanced functional activity by expressing Atoh1 (Hath1) from an Ad28GFAP vector as compared to Ad5 (subgroup C) based vector documented in the Declaration filed on 12/17/2009 (as well as related declaration filed on 02/26/2009) have been fully considered and found not persuasive because subgroup D (Ad28) adenoviral vectors were developed later to overcome the issues researchers had experienced with subgroup C (Ad5) mediated gene expression for genes therapy purposes. This has been specifically taught by Falck-Pedersen et al. (See lines 34-40, column 6, Falck-Pedersen et al.) and thereby the asserted "unexpected results" are, in fact, exactly as expceted by the teachings of cited prior arts in the 103 rejections documented in this office action.

The following statements and case laws are relevant to declaration under 37 CFR 1.132 as evidence of non-obviousness.

"Appellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992).

An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979)

MPEP 716.03(g). "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. *Ex parte Gray*, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative.

Conclusion

9. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632